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Research Article

Correlation of Cystic Fibrosis Mutations and Pulmonary Function Tests in a Tertiary Care Centre

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Abstract

Introduction: The severity of pulmonary disease has been reported to some extent to be predicted by the cystic fibrosis transmembrane regulator gene mutations (CFTR). Knowledge of this relationship may predict the prognosis and provides modality of treatment that can be offered to improve survival.

Objectives: To investigate the correlation of Pulmonary Function Tests (PFT) and CFTR mutations in our CF population during their follow up period.

Methodology: A review of CF patients' records from the period 1984 - 2018. All PFT parameters at presentation and at last follow up were correlated with their CFTR gene.

Results: A total of 182 patients had their PFT done at the first visit at a mean age 9.7 (5.2) and 153 patients had their PFT at last follow up visit at a mean age of 17.8 (7.2) years. There was a decline in all PFT patterns in all types of CFTR gene mutations, namely: p.G473EfsX54, 3120+1G>A, DF508, p.H139L, 711+1G>T, p.N1303K, and p.S549R, with P value: < 0.05. Only 2 mutations showed improvement or mild deterioration in PFT parameters at follow-up period namely:(p.Q637HfsX26 and p.I1234V) mutations, with P value: < 0.05. Regarding the severity of PFT, there were 85/182 (46.7%) who had assessment of First PFT, found to have normal pattern, whereas 97/182(53.3%) had mild to severe PFT changes, (P Value 0.104). The assessment of PFT severity at follow up of 7 years' period showed 42/153 (27.45%) had normal PFT compared to 111/153 (72.55%) of follow-up PFT to have mild to severe changes respectively (P Value 0.0735).

Conclusion: All Saudi CFTR gene mutation in CF patients showed deterioration in all PFT variables patterns at follow up. Only 2 CFTR mutation showed PFT improvement. Physician should monitor PFT during follow-up period and be aware of this correlation to provide appropriate interventions and prevent PFT deterioration.

Keywords: *Cystic Fibrosis; PFT; CFTR; FEV1; Obstructive Lung Disease; Restrictive Lung Disease*

Abbreviations

PFT: Pulmonary Function Test; CF: Cystic Fibrosis; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the First Second; FEV0;75: Forced Expiratory Volume in the First 0;75 Second; FEV0;50: Forced Expiratory Volume in the First 0;50 Second; FEV1/FVC: Forced Expiratory Volume in the First Second - Forced Vital Capacity Ratio; FEF25-75%: Mean Forced Expiratory Flow Between 25% and 75% of Total Forced Expiratory Volume; Vmax FRC: Maximal Flow at Functional Residual Capacity; FRC: Functional Residual Capacity; RV: Residual Volume; TLC: Total Lung Capacity; RV/TLC: Residual Volume - Total Lung Capacity Ratio; MCh: Methacholine; *P. aeruginosa*:

Pseudomonas aeruginosa; ICS: Inhaled Corticosteroids; GI: Gastrointestinal Manifestations; CFTR: Cystic Fibrosis Transmembrane Regulator Gene; MRSA: Methicillin-Resistant *Staphylococcus aureus*; NTM: Nontuberculous Mycobacteria

Introduction

Advances in the early detection of cystic fibrosis (CF) lung disease have contributed to a better understanding of its pathophysiology over the last decade. Mucous plugging contributes to bronchial dilatation [1,2]. Inflammatory process was demonstrated before appearance of bronchiectasis [3-8].

Castile., *et al*. [9] described the PFT measurements using the raised-volume rapid thoraco-abdominal compression technique and incentive spirometry and were carefully conducted based on standardized, published guidelines [9].

The physiological measure: FEV at 0.5 second (FEV0.5) differentiated children with CF from healthy controls during infancy, not during preschool years [10].

Castile., *et al*. [9] described that the *Pseudomonas aeruginosa* (*P. aeruginosa*) infection, wheezing, and recent cough was related to reduced lung function even after it's eradication.

Levine., *et al*. [11] described the relationship of bronchospasm with the inflammatory process that led to decreased Vmax FRC (Maximal flow at functional residual capacity) and became normal with metapropranolol [12-15]. Similarly, Sanchez., *et al*. reported that 40% of CF children with mild CF developed moderate to severe obstructive pattern [16]. A different study of 4480 CF children showed that childhood wheezing is associated with lower PFT parameters [17]. Another study showed a hypercontracted state of human airway smooth muscle [18,19].

Hyper responsiveness airway with CF is common specially in those with a positive methacholine (MCh) challenge test [12,20,21]. Mitchell., *et al*. [22] described a positive response to (MCh) in half of CF patients with a unique pathophysiologic mechanism [22].

As there is no previous research that show the PFT changes of CF population in Saudi Arabia, we carried out this study to investigate the correlation of PFT and CFTR mutations in our CF population during their follow up period.

Materials and Methods

A review of CF patients' records from the period 1984 - 2018. All PFT parameters at presentation and at last follow up were correlated with their CFTR gene.

CFTR Identification: As mentioned before in previous study [23].

PFT measurement

Measurement of the spirometry and lung volume were used including: Forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and forced expiratory flow in the middle half of FVC at age > 6 years according to the criteria established by the American Thoracic Society [24]. The percent of the predicted values, based on height and sex, were used for all analyses [24].

PFT (1): as first PFT. PFT (2): as PFT done at last follow up during the study period.

Severity of PFT:

The severity of each variable of spirometry abnormalities in this study was based on World Health Organization (WHO) guidelines [25] as the following:

- **Normal degree:** Forced expiratory volume in the first second (FEV1) equal or ≥ 80% predicted.
- **Mild degree:** (FEV1) equal > 70 - 79% predicted.
- **Moderate degree:** (FEV1) is 60 - 69% predicted.
- **Moderately severe degree:** (FEV1) is 50 - 59% predicted.
- **Severe degree:** (FEV1) is 35 - 49% predicted.
- **Very severe degree:** (FEV1) is < 35% predicted.

Ethical considerations

The ethical approval by the research advisory committee was obtained, and the Declaration of Helsinki and good clinical practice guidelines were followed. All data were accessed only by the principal investigator and the assigned personnel. All patient's information kept strictly confidential. The department of Biostatistics Epidemiology and Scientific Computing (BESC) carried out statistical analysis of the data.

Statistical method: variables were described by means, and standard deviations. Categorical variables were calculated by frequencies and percentages. Assessment of the differences between first and last PFT measurements were done by Paired T-test or Wilcoxon signed test. The relationships between PFT and mutations were calculated by Chi-square test, while McNemar's test was used to assess the difference in severity between first and last PFT parameters. A P value of < 0.05 was considered as the level of significance. Analysis of data was done by JMP 15.0 from SAS. T-Test was used for continuous variables, to calculate the mean, standard deviation and median.

Results

A total of 182 patients had their PFT done at the first visit at a mean age 9.7 (5.2) and 153 patients had their last PFT parameters at a mean age of 17.8 (7.2) years. There was a decline in all PFT patterns in all types of CFTR gene mutations, namely: p.G473EfsX54, 3120+1G>A, DF508, p.H139L, 711+1G>T, p.N1303K, and p.S549R (worsening group), (P Value: < 0.05).

The range of median for the (worsening group) that were mentioned earlier for all PFT variables at first PFT compared to last follow up PFT were as the following: Forced vital capacity (FVC) % Predicted (70.5 - 87)/(50.1 - 77.2), Forced Expiratory Volume in One Second (FEV1)% Predicted (48.09 - 87)/(39.6 - 77.6), Peak Expiratory Flow (PEF)% Predicted (33.9 - 115.2)/(26.2 - 104), Maximal mid-expiratory flow (MMEF (75 - 25%) Predicted (45 - 102.4)/(18.7 - 64.3), intrathoracic gas volume (ITGV) % Predicted (104.2 - 147)/(100.3 - 185.7), Residual Volume (RV) % Predicted (188.8 - 112.3)/(140.5 - 250.9), Total Lung Capacity (TLC) % Predicted (64 - 102.6)/(74.4 - 110), (RV/TLC) % Predicted (125.7 - 198)/(102.5 - 279.6), (P Value: < 0.05), (Table 1).

Only 2 mutations showed improvement or mild deterioration in PFT parameters at follow-up period (Improving group) namely: (p.Q637HfsX26 and p.I1234V) mutations, with P value: < 0.05.

The range of median of the (Improving group) for all PFT variables at first PFT compared to last follow up PFT were as the following: Forced vital capacity (FVC) % Predicted (73.25 - 81.5)/(78.1 - 79.2), Forced Expiratory Volume in One Second (FEV1)% Predicted (78 -

86)/(78.6 - 81.3), Peak Expiratory Flow (PEF)% Predicted (97.55 - 74.9)/(75.8), Maximal mid-expiratory flow between 25% and 75% (MMEF (75 - 25%)) % Predicted (67 - 92.6)/(53.6 - 63.1), intrathoracic gas volume (ITGV) % Predicted (98.7 - 106.7)/(108.1 - 139.3), Residual Volume (RV) % Predicted (108.9 - 114.4)/(109.9 - 125.8), Total Lung Capacity (TLC) % Predicted (83.4 - 87.7)/(77.7 - 100), (RV/TLC) % Predicted (110.6 - 142.7)/(156.2 - 161.4), (P Value: < 0.05) (Table 1).

CFTR mutation	Nucleotide Change	Legacy name	refSNP	PFT (1) Total number= 182 Median values								PFT (2) Total number= 153 Median values							
				FVC % Predicted	FEV1 % Predicted	PEF % Predicted	MMEF(25-75) % Predicted	ITGV % Predicted	RV % Predicted	TLC % Predicted	RV/TLC % Predicted	FVC % Predicted	FEV1 % Predicted	PEF % Predicted	MMEF(25-75) % Predicted	ITGV % Predicted	RV % Predicted	TLC % Predicted	RV/TLC % Predicted
p.Phe508del[W]	c.1521_1523delCTT	[delta]F508; Exon 10	rs113993960	81	79.04	115.2	54	104.2	152	98.9	198	72.9	64.9	26.2	47.1	110.1	154.5	99.5	193.4
711+1G>T[W]	c.579+1G>T	711+1G>T: Intron 5	rs77188391	70.5	74.07	61.4	70.80	142.3	178.5	102.6	190	66.9	61.4	39	51.2	185.7	250.9	107.8	212
3120+1G>A[W]	c.2988+1G>A	3120+1G>A; Intron 16	rs75096551	57	48.09	-	45	141.8	151.5	84.5	185	50.1	39.6	-	18.7	100.3	172	74.4	221.5
p.Gly473GlufsX54[W]	c.1418delG	1548delG; Exon 10	rs397508205	71.45	75	83.4	67.65	106	134	91.2	125.7	55.08	54.2	85.9	38.8	120	205.1	85.6	219.15
p.His139Leu[W]	c.416A>T	H139L; Exon 4	rs76371115	85.3	85.95	33.9	71.70	116.4	188.8	89.5	164.6	68	52.5	104	56.30	143	245	110	279.6
N1303K; Exon 21[W]	c.3909C>G	N1303K; Exon 21	rs80034486	87	87	95.4	102.4	147	147	64	**22**	77.2	77.6	56.2	64.3	170.4	140.5	96.9	102.5
p.Ser549Arg[W]	c.1647T>G	S549R 'T>G'; Exon 12	rs121909005	85.5	85	85	46	107.6	112.3	87.1	132.8	69.5	47.4	65	19.9	120.3	197.6	101.5	217
Others[W]				77.1	78	63.3	61.6	146	158.1	97.4	159.75	71	74	97	55	156	219.7	98.7	254
p.Ile1234Val[I]	c.3700A>G	I1234V; Exon 19	rs75389940	81.5	86	97.55	92.6	98.7	108.9	87.7	110.6	78.1	81.3	75.8	63.1	108.1	125.8	77.7	161.4
p.Gln637Hisfs[I]	c.1911delG	2043delG; Exon 13	rs1554389296	73.25	78	74.9	67	106.7	114.4	83.4	142.7	79.2	78.6	70	53.6	139.3	109.9	100	156.2
PFT(1)/PFT(2) P Values	[W]: Worsening group			0.0030	<0.0001	0.6299	<0.0001	0.0433	0.0419	0.1212	0.0429								
	[I]: Improving group			0.0565	0.0002	-	0.0007	0.2401	0.2648	0.3844	0.6777								

Table 1: *Pattern of PFT (1) at presentation and last follow up PFT (3)182/153*

Legend*: - #= number, FEV1: Forced Expiratory Volume In One Second; TLC: Total Lung Capacity, PEF: Peak Expiratory Flow. FEV1/FVC: Forced expiratory volume in the first second/Forced vital capacity ratio. MMEF (75-25%): Maximal mid-expiratory flow between 25% and 75% of total force expiratory volume. RV: Residual Volume. RV/TLC: Residual Volume/Total lung capacity ratio. PEF: Peak Expiratory flow. N: Number of cases. NA: Not applicable. SE: Standard Error. PFT: Pulmonary Function Test. PFT(1): First Pulmonary Function Test. PFT(2): Pulmonary Function Test at Last follow up. %: Percentage. CFTR: Cystic Fibrosis Transmembrane Regulator. Ref: References. refSNP: Reference Single Nucleotide Polymorphism Database, https://www.ncbi.nlm.nih.gov/snp/, [W]: Worsening group, [I]: Improving group, PFT(1)/PFT(2) P Values: Comparison of each PFT variable of worsening compared to improving group.*

Of 182 patients who were assessed for PFT patterns at first PFT; 64 (35.17%) had normal PFT, and 118 (64.83%) had abnormal PFT compared to 72 (47.06%) and 81 (52.94%) of PFT at follow up respectively. (Table 2).

There data showed a progressive reduction in all the percentage predicted values of (FVC, FEV1, MMEF (25% - 75%) and PEF) over the follow up period of seven years in the (Worsening group), comparing the PFT abnormalities of the (Improving group) and the (worsening group) during the first and last follow up PFT; we found that there were increasing numbers of normal PFT at follow up in the (Improving group) compared to a decreasing numbers of the normal PFT in the (worsening group), (P Value < 0.0735) (Table 2).

CFTR N (%)	TYPES OF PFT									
	PFT (1) N:182					PFT (2) N:153				
	Normal N= 64 (35.17)	Abnormal N=118 (64.83)			Total	Normal N = 72 (47.06)	Abnormal N= 81 (52.94)			Total
		Obstructive	Restrictive	Combined			Obstructive	Restrictive	Combined	
p.Phe508del	5 (35.71)	4 (28.57)	3 (21.43)	2 (14.29)	14	5 (41.7)	4 (33.3)	2 (16.7)	1 (8.3)	12
711+1G>T	6 (35.29)	6 (35.29)	3 (17.65)	2 (11.75)	17	9 (60)	5 (33.3)	1 (6.7)	0 (0)	15
3120+1G>A	8 (57.14)	2 (14.29)	1 (7.14)	3 (21.43)	14	7 (77.8)	2 (22.2)	0 (0)	0 (0)	9
p.G473EfsX54	8 (25)	16 (50)	3 (9.38)	5 (15.62)	32	14 (46.7)	8 (26.7)	4 (13.3)	4 (13.3)	30
p.H139L	10 (52.63)	7 (36.84)	1 (5.26)	1 (5.26)	19	7 (46.7)	2 (13.3)	4 (26.7)	2 (13.3)	15
p.N1303K	1 (14.3)	4 (57.1)	2 (28.6)	0 (0)	7	0 (0)	2 (40)	1 (20)	2 (40)	5
p.S549R	3 (42.9)	2 (28.6)	1 (14.3)	1 (14.3)	7	3 (42.9)	2 (28.6)	2 (28.6)	0 (00)	7
Others	11 (37.93)	13 (44.83)	3 (10.34)	2 (6.9)	29	10 (43.5)	11 (47.8)	1 (4.35)	1 (4.35)	23
p.I1234V	11 (33.3)	16 (48.5)	4 (12.1)	2 (6.1)	33	16 (59.3)	6 (22.2)	3 (11.1)	2 (7.4)	27
p.Q637HfsX26	1 (10)	5 (50)	4 (40)	0 (0)	10	1 (10)	4 (40)	5 (50)	0 (0)	10
Total #(%)	64 (35.17)	118 (64.83)			182	72 (47.06)	81 (52.94)			153
	P value: 0.0737					P value: 0.0737				

Table 2: *Types of pft at presentaion (pft 1) and at last follow up (pft 3), Total (182/153).*

Legend*: - PFT: Pulmonary Function Test. PFT(1): First Pulmonary Function Test. PFT(2): Pulmonary Function Test at Last follow up. %: Percentage. CFTR: Cystic Fibrosis Transmembrane Regulator. N: Number of patients. %: Percentage.*

Similarly, comparison of the severity of first PFT and last PFT; all CFTR groups showed that there was persistent involvement of all degree of severity in PFT across all CFTR mutations but to a lesser degree in the (Improving group), P Value 0.0735 (Table 3).

Regarding the severity of PFT, there were 85/182 (46.7%) who had assessment of First PFT, found to have normal pattern, whereas 97/182(53.3%) had mild to severe PFT changes, (P Value 0.104). The assessment of PFT severity at follow up of 7 years' period showed 42/153 (27.45%) had normal PFT compared to 111/153 (72.55%) of follow-up PFT to have mild to severe changes respectively (P Value 0.0735) (Table 3).

	PFT (1)							PFT (2)						
Count Total (%)	Normal #: 85 (46.7)	Abnormal Total number= 97 (53.3)					Total	Normal #: 42 (27.45)	Abnormal Total number= 111 (72.55)					Total
		Mild	Moderate	Moderate severe	Severe	Very severe			Mild	Moderate	Moderate severe	Severe	Very severe	
p.Phe508del	4 (28.6)	4 (28.6)	1 (7.1)	3 (21.4)	2 (14.3)	0 (0)	14 7.6	4 (33.3)	2 (16.7)	2 (16.7)	0 (0)	3 (25)	1 (8.3)	12 7.8
711+1G>T	7 (43.8)	3 (18.8)	3 (18.8)	0 (0)	2 (12.5)	1 (6.3)	16 8.7	3 (20)	3 (20)	2 (13.3)	2 (13.3)	2 (13.3)	3 (20)	15 9.8
3120+1G>A	3 (21.4)	1 (7.1)	2 (14.3)	2 (14.3)	6 (42.9)	0 (0)	14 7.6	1 (10)	1 (10)	2 (20)	0 (0)	2 (20)	4 (40)	10 6.5
p.G473EfsX54	17 (51.5)	2 (6.1)	4 (12.1)	6 (18.2)	2 (6.1)	2 (6.1)	33 17.9	6 (20.7)	5 (17.2)	3 (10.3)	4 (13.8)	6 (20.7)	5 (17.2)	29 18.9
p.H139L	11 (57.9)	2 (10.5)	3 (15.8)	1 (5.3)	2 (10.5)	0 (0)	19 10.3	3 (21.4)	2 (14.3)	2 (14.3)	2 (14.3)	2 (14.3)	3 (21.4)	14 9.1
p.N1303K	5 (71.4)	1 (14.3)	1 (14.3)	0 (0)	0 (0)	0 (0)	7 3.8	2 (40)	2 (40)	0 (0)	0 (0)	0 (0)	1 (20)	5 3.3
p.S549R	2 (28.6)	2 (28.6)	0 (0)	1 (14.3)	1 (14.3)	1 (14.3)	7 3.8	1 (14.3)	1 (14.3)	0 (0)	1 (14.3)	2 (28.6)	2 (28.6)	7 4.6
Others	12 (42.8)	5 (17.9)	3 (10.7)	4 (14.3)	4 (14.3)	0 (0)	28 15.4	7 (30.4)	6 (26.1)	1 (4.3)	4 (17.4)	3 (13.1)	2 (8.7)	23 15
p.I1234V	20 (58.8)	7 (20.6)	2 (5.9)	1 (2.9)	2 (5.9)	2 (5.9)	34 18.5	13 (46.4)	3 (10.7)	3 (10.7)	1 (3.6)	2 (7.1)	6 (21.4)	28 18.3
p.Q637HfsX26	4 (40)	5 (50)	0 (0)	1 (10)	0 (0)	0 (0)	10 5.4	2 (20)	4 (40)	2 (20)	0 (0)	1 (10)	1 (10)	10 6.5
Total	85 (46.7)	32 (17.4)	19 (10.3)	19 (10.3)	21 (11.4)	6 (3.3)	182	42 (27.45)	29 (18.8)	17 11	14 9.1	23 14.9	28 18.2	153
		97 (53.3)							111 (72.55)					
P Value	0.1042							0.0735						

***Table 3**: Severity of PFT at presentation PFT (1) and at last follow up PFT (3), 182/153.*

***Legend**: PFT: Pulmonary Function Test. PFT(1): First Pulmonary Function Test. PFT(3): Pulmonary Function Test at Last follow up. %: Percentage. CFTR: Cystic Fibrosis Transmembrane Regulator. #: Number of patients. %: Percentage.*

Discussion

Kraemer., *et al*. [26] discussed the correlation between the signs and symptoms, and PFT in 60 CF infants (33 females, 27 males) at the time of diagnosis (age: 7 months) [26] by using infant's whole-body plethysmography. Age at time of diagnosis was independent from the genotype. Differences regarding lung function within the genetic groups are mainly related to pulmonary hyperinflation, measured by thoracic gas volume (TGV), present in 8 out of 9 infants with 3905insT, differentiating this frameshift mutation (TGV of 7.0 (3.6)) from the R553X mutation (TGV 2.1 (4.6); $p < 0.02$). The conclusion of the clinical variations and PFT reflected by features already presented at the time of diagnosis, but the lungs hyperinflation is partly influenced by the CFTR mutations [26].

Our study did not include patients less than 5 years due to comprehensive difficulties to PFT maneuvers as it is only tailored to age > 5 years.

Also, we have shown that there were progressive PFT deterioration in all CFTR mutations (Worsening group) except two of them that were considered mild mutations (Improving group) with more patients reported with pancreatic sufficiency and near normal growth as in (p.Q637HfsX26 and p.I1234V) [27,28].

Schaedel., *et al*. [29] found no differences in PFT between males and females, but was unclear it was related to the CFTR or not. Patients were subdivided into four CFTR groups: A slower rate of decline of FEV1 in patients with missense mutations compared with the other CFTR types (P Value = 0.01). Patients with diabetes mellitus had a quick decline in FEV1 (P Value = 0.02). No difference in PFT parameters between patients with and without liver cirrhosis (P Value = 0.84). He found that CFTR genotypes associated with long-term pancreatic sufficiency have mild lung disease and better PFT parameters. A lower incidence of chronic Pseudomonas colonization was found in patients with missense mutations and in patients with pancreatic sufficiency, which indicates that PA infection is affected by the CFTR mutations [30]. Other studies described no difference in annual decline of FEV1 between PS patients with and without PA colonization [31,32].

Our study did not study any morbid factors that mentioned in Schaedel study and planned to identify such relationship.

Garcia., *et al*. [32] divided the 120 adult CF patients into two groups according to whether the CFTR protein reached the epithelial cell surface (presence of at least one mutation class type III, IV or V) or not (presence of type I or II mutation class on both chromosomes) [32].

There mean FVC and FEV1 predicted values were significantly higher in patients with genotype I-II/I-II. The lung disease was different between patients with genotype I-II/I-II and those with class III, IV or V CFTR mutations on at least one chromosome. Patients with CFTR class I or II on both chromosomes had a significant decrease in PFT parameters during follow up than patients with class III, IV or V CFTR mutations (P = 0.04). Other factors may have played a role in PFT deterioration such as type of bacterial cultures, compliance to medications and mucous clearance [32].

In our study, most of the CFTR of the worsening group are from class I and II, and those from improving group are from class IV and V [33-35].

Conclusion

Our Saudi CFTR population showed deterioration in all PFT variables except of (p.Q637HfsX26 and p.I1234V).

Conflict of Interest

No conflict of interest between authors.

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